Exploring the Role of Transcatheter Aortic Valve Replacement as the Preferred Treatment for Lower-Risk Patients

The investigators of the NOTION (Nordic Aortic Valve Intervention) trial showed that in an all-comers population of patients with severe aortic stenosis, transcatheter aortic valve replacement (TAVR) using the CoreValve self-expanding bioprosthesis (Medtronic Inc., Minneapolis, Minnesota) yielded similar rates of the composite endpoint of all-cause death, stroke, or myocardial infarction at 1 year compared with surgical bioprosthetic aortic valve replacement (1). Their study is the first to assess in a randomized trial the results of TAVR in a population including a high proportion of patients with low surgical risk (81.8% of patients). The scope of their findings paves the way toward the expanded use of TAVR, from extreme- to high-risk patients (2–5) to patients bearing lower surgical risks. However, the results of the primary analysis do not allow comment on the effects of TAVR among low-risk population. As the CoreValve trial taught (5), high-risk patients undergoing a self-expandable TAVR yield better outcomes (lower mortality) than with surgical bioprosthetic aortic valve replacement. It is likely that, among both groups of the NOTION trial, adverse events were concentrated in the minority of moderate- to high-risk patients, mirroring the results of the high-risk CoreValve trial. Consequently, clinical equipoise, with low event rates in both groups, is more than likely among their low-risk patient population. Although Thyregod et al. have to be commended for their pioneer work, this information is currently not available in their report. Obviously, with only 280 enrolled patients, the current trial lacks power to identify significant differences among important subgroups; however, to provide the rates of adverse events between TAVR and surgical bioprosthetic aortic valve replacement among their low-risk population would be highly informative, potentially disruptive, and could help to foster future investigations. Although ongoing trials (PARTNER IIA [Placement of AoRTIc TraNscathetER Valves] [NCT01314313], SURTAVI [Safety and Efficacy Study of the Medtronic Corevalve System in the Treatment of Severe, Symptomatic Aortic Stenosis in Intermediate Risk Subjects Who Need Aortic Valve Replacement] [NCT01586910]) will bring more definitive answers related to the place of TAVR in the treatment of lower-risk patients, the authors are encouraged to provide additional analysis of the primary outcome in patients according to their surgical risks.

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REPLY: Exploring the Role of Transcatheter Aortic Valve Replacement as the Preferred Treatment for Lower-Risk Patients

In the NOTION (Nordic Aortic Valve Intervention) trial (1), we included all eligible patients with stand-alone severe aortic valve stenosis. This resulted in a patient population with a mean Society of Thoracic Surgeons Predicted Risk of Mortality score of 3.0% and 82% considered at low surgical mortality risk (a score lower than 4%). The 2 other randomized trials comparing transcatheter aortic valve replacement versus surgical aortic valve replacement included high-risk patients with a mean Society of Thoracic Surgeons Predicted Risk of Mortality score of 11.7% (2) and 7.4% (3). As noted by Drs. Gravel and Généreux, the outcomes of our trial could potentially be driven by outcomes primarily in intermediate- and high-risk patients, constituting 18% of the sample size, and would therefore not reflect results for true low-risk patients. However, this was not what we found as will be demonstrated in an upcoming publication of the NOTION trial 2-year results.

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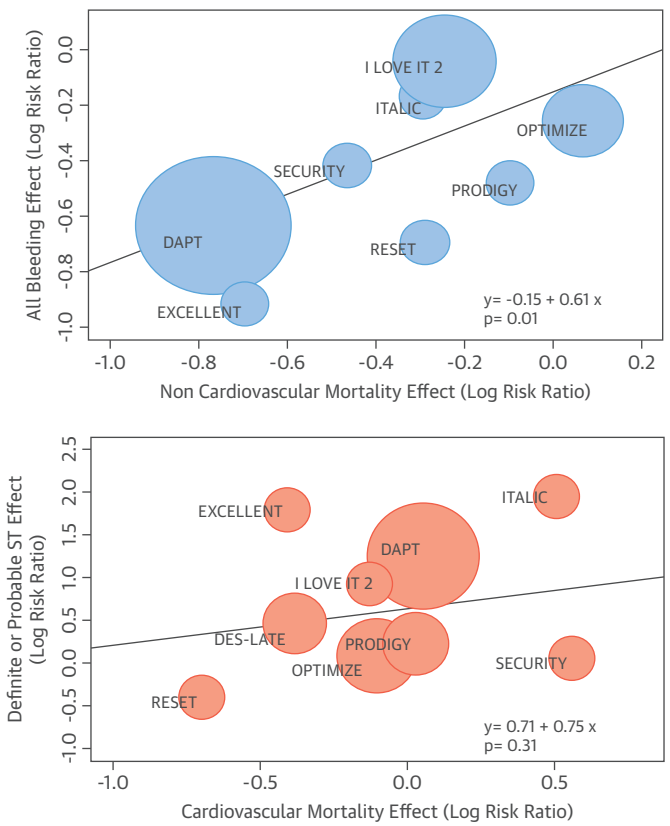
Meta-Analyses of Dual Antiplatelet Therapy Following Drug-Eluting Stent Implantation

Do Bleeding and Stent Thrombosis Weigh Similar on Mortality?

We read with interest the meta-analyses of Giustino et al. (1) and Palmerini et al. (2) recently published in the *Journal*. These studies add meaningfully to the ongoing debate on dual antiplatelet therapy (DAPT) duration, but their conclusions on mortality are conflicting, with Giustino et al. (1) concluding that prolonging DAPT increases all-cause mortality and Palmerini et al. (2) demonstrating no significant effect on this endpoint. Indeed, addressing the net benefit of extended DAPT requires preliminary clarification of the relative weights of stent thrombosis (ST) and bleeding on mortality, an issue that has not been explored by any trial or meta-analysis of DAPT duration. We hypothesized that in the contemporary era of drug-eluting stents, ST and bleeding have a different impact on mortality. To explore this hypothesis, we performed a meta-regression of the effects sizes of ST and bleeding on mortality in trials of DAPT duration, including the recently presented I-LOVE-IT (Evaluate Safety and Effectiveness of the Tivoli DES and the Firebird DES for Treatment of Coronary) 2 randomized substudy (China Interventional Therapeutics, March 19, 2015, Beijing, China). Trials were excluded if the outcomes of interest were not available. Risk ratios for treatment effects in individual trials were log-transformed before being used as independent variables in linear meta-regression analyses. Statistical analyses were performed using the open-source R Software (R Foundation for Statistical Computing, Vienna, Austria). We found a significant association between all bleeding and noncardiovascular mortality across individual studies (8 trials; intercept value [IV]: -0.15; slope estimate [SE]: 0.61; $p = 0.01$) (**Figure 1**, top graph), while there was no evidence of a significant correlation of all bleeding with both cardiovascular (8 trials; IV: -0.46; SE: -0.17; $p = 0.69$) and all-cause mortality (10 trials; IV: -0.33; SE: 0.75; $p = 0.18$). On the other hand, no significant associations were found between ST and both cardiovascular (9 trials; IV: 0.75;

FIGURE 1 Association Between Log-Transformed Risk of All Bleeding and ST With Noncardiovascular and Cardiovascular Mortality, Respectively



The **size of each circle** represents the precision of each estimate (the inverse variance of the log relative risk in the trial), and the line is the best fit for the metaregression model.